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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,659	07/09/2003	Costas D. Maranas	P06367US03	9959

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EXAMINER	
SKOWRONEK, KARLHEINZ R	

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
11/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/616,659	MARANAS ET AL.	
	Examiner	Art Unit	
	KARLHEINZ R. SKOWRONEK	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *6,9 and 15-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8,10-14 and 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-22 are pending.

Claims 6, 9, and 15-17 are withdrawn as being directed to a non-elected species as indicated in the response, filed 07 April 2006, to the Office Action dated 20 March 2006.

Claims 1-5, 7-8, 10-14, and 18-22 have been examined.

Claims 1-5, 7-8, 10-14, and 18-22 are rejected.

Priority

The instant application claims priority to provisional application No. 60/395,763, filed 10 July 2002; provisional Application No. 60/417,511, filed 9 October 2002; and Provisional Application No. 60/444,933, filed 3 February 2003.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5, 7-8, 10-14, and 18-22 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-5, 7-8, 10-14, and 18-22 are directed to processes of predicting genes for deletion in model of metabolism for an organism. The following analysis is taken from the guidance provided in the MPEP at 2104.IV, "Determine Whether the Claimed Invention Complies with 35 USC101". The claims are directed to processes. Here the

claims are directed to the abstract idea of making a gene deletion prediction on the basis of a mathematical representation of the metabolism for an organism. The processes do not recite a physical transformation of matter from one state to another. Giving the claims the broadest reasonable interpretation, the claims read on mental steps. In *Comiskey* (*In re Comiskey*, 84 USPQ2d 1670) the court established that "the application of human intelligence to the solution of practical problems is not and of itself patentable" (at 1680). In *Comiskey*, the court stated explicitly "mental processes - or processes of human thinking - standing alone are not patentable even if they have a practical application" (at 1679). The court in *Comiskey* stated, "Following the lead of the Supreme Court, this court and our predecessor court have refused to find processes patentable when they merely claimed a mental process standing alone and untied to another category of statutory subject matter even when a practical application was claimed" (at 1680). In the instant claims, the process is not tied to a class of statutory invention.

Claims 1-5, 7-8, 10-14, and 18-22 recite providing an output or a response to a user. The output is insignificant post-solution activity and does not represent a significant tie to another category of invention. The court in *Comiskey*, stated "the court rejected the notion that mere recitation of a practical application of an abstract idea makes it patentable, concluding that '[a] competent draftsman could attach some form of post-solution activity to almost any mathematical formula'" citing *Flook* (437 U.S. at 586, 590). Applicant is encouraged to consider the recent BPAI informative decisions

Exparte Langemyr (No. 2008-1495 (28 May 2008)) and *Exparte Biliski* (No. 2002-2257 (26 September 2006)) for further clarification of the above grounds of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. (IDS entry 2, 8 May 2007), in view of Bhaska et al. (Reviews in Chemical Engineering, Volume 16, Issue 1, p. 1-54, 2000).

The claims are drawn to a method comprising selecting a bioengineering objective function; selecting a cellular objective function forming a linear optimization problem that couples the cellular objective function with the bioengineering objective function; and solving the linear optimization problem to yield a candidate. In some embodiments, the optimization problem includes a binary value for specifying if a flux is active or inactive. In some embodiments, the bioengineering function is over production of a chemical being directed to the relative overproduction of phenylalanine. In some embodiments, the optimization problem includes an uptake constraint. In some embodiments, the performance limits are evaluated on the ability to meet the at least objective function.

Hatzimanikatis et al. shows that objective functions can be formed for any process of interest (p. 1281, col. 2). Hatzimanikatis et al. shows improvements in the product yield, rate of production, and final product concentration are common goals in achieving more efficient and cost-effective bioprocesses (p. 1277, col. 1). Hatzimanikatis et al. shows prior research and industrial practice have clearly shown that very large increases in process performance can be realized by genetic modifications of metabolic control systems (p. 1278, col. 1). Hatzimanikatis et al. shows guidance as to what changes in regulation might be of greatest benefit to improve the network is important (p. 1278, col. 1). Hatzimanikatis et al. shows that objective

functions can be formed for any process of interest (p. 1281, col. 2). Hatzimanikatis et al. shows a bioengineering objective function in eqn. 32 relating to the production phenylalanine (p.1284, col. 1). Hatzimanikatis et al. suggests that cellular growth rate can be defined as an objective function (p. 1278, col. 1). In an embodiment, Hatzimanikatis et al. shows the optimization problem includes a binary value for specifying if a flux is active or inactive (p. 1282, col. 2). In an embodiment, Hatzimanikatis et al. show the bioengineering function is over production of a chemical being directed to the relative overproduction of phenylalanine (p.1284, col. 1). In an embodiment, Hatzimanikatis et al. shows the optimization problem includes an uptake constraint (p.1284, col. 1). In an embodiment, Hatzimanikatis et al. shows the optimization problem includes a stoichiometric constraint (p. 1282, col. 1). In an embodiment, Hatzimanikatis et al. shows the performance limits are evaluated on the ability to meet the at least objective function (p. 1279, col. 1). Hatzimanikatis et al. shows that no improvement in the selectivity for the reference state could be achieved only by enzyme overexpression, without having an effect on the growth rate (p. 1284, col. 2). Thus, Hatzimanikatis et al. suggest growth rate is coupled to amino acid production.

Hatzimanikatis et al. does not show the cellular and bioengineering objective functions that are coupled in a single optimization problem.

Bhaskar et al. shows that multiple objective optimization is applied to biochemical engineering problems such as the design of anaerobic digesters (table 1). Bhaskar et al. shows that most real world chemical engineering problems require the simultaneous

optimization of several objectives (multi-objective optimization) which cannot be compared easily with each other (are non-commensurate), and so cannot be combined into a single, meaningful scalar objective function (p. 4). Bhaskar et al. shows that objective functions can be coupled through a dual problem such that the dual objective function is always bound to the original objective function called the primal (also known as bi-level)(p. 4-5). Bhaskar et al. shows that if the optimal dual objective function result is identified then the primal objective function result has also been identified (p. 5). Bhaskar et al. show the bi-level optimization programming in a simple problem demonstrates the opposing results of a reaction in which the maximum yield and selectivity of a chemical reaction are sought Bhaskar et al. shows that the between points P and Q both functions approach a maximum at Q. Between Q and R, Bhaskar et al. shows that while selectivity increases, the yield decreases (figure 2). Thus Bhaskar et al. shows that optimal solutions can be found in divergent objective functions.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the linear programming and objective functions to predict metabolic pathway alterations of Hatzimanikatis et al. with the multi-objective optimization and dual/primal optimization problems of Bhaskar et al. to produce optimization problem that balances the goals of bioengineering and cellular outputs because the technique of bi-level optimization and it's ability to couple objective functions was recognized as part of the ordinary capabilities of one skilled in the art. One of skill in the art would have been capable of applying bi-level optimization to an optimization problem and the results would have been predictable to one of skill in the

art. This is also supported by applicant's statement, "the referenced duality theory concepts were well known to those skilled in the art" (see remarks p.6, filed 31 October 2007). It would have been further obvious to modify the MILP formulation of Hatzimanikatis et al. to express the MILP formulation as bi-level programming problem to identify key enzymes that are capable of regulating or modifying the flux of a metabolism to produce a product because Hatzimanikatis et al. shows metabolite production is coupled to cell growth. One of ordinary skill in the art would have been motivated to find genetic modifications, whether gene deletions or additions, that would allow the maximal production of any commercially relevant metabolite product such that growth rate or some other cellular objective is maximized because an organism having such properties would provide the benefit of higher product yields at lower growth costs.

Response to Arguments

Applicant's arguments filed 05 August 2008 have been fully considered but they are not persuasive. Applicant argues Hatzimanikatis et al. is directed to modification of metabolic pathway regulatory control structures and teaches away from defining a linear optimization problem that couples a cellular objective with a bioengineering objective function. The arguments with respect to Hatzimanikatis et al. are not persuasive. First, Hatzimanikatis et al. uses the term regulation to describe both the control of enzyme expression and the control of enzyme activity. Specifically, Hatzimanikatis et al. summarizes what is known well known in the art and those of ordinary skill, stating "All the major cellular pathways are subject to a collection of natural independent control loops with different signals and different loci of action. These mechanisms of metabolic

regulation operate at essentially two different levels. Genetic-level controls regulate the expression of genes, thereby determining which enzymes are present and in what quantity. Protein-level controls regulate the activity of particular enzymes and other proteins in the cell (p. 1277, col. 2). Hatzimanikatis et al. provides a mathematical description of a metabolic pathway with a postulated number of regulatory loops, where the loops are classified as either activation (increase in the activity of the regulatory enzyme) or inhibition (decrease in the activity of the regulatory enzyme) loops (p. 1279, col. 1). In the context the Hatzimanikatis et al. mathematical description of the metabolic pathway, the use of regulatory refers to protein level control, in which an enzyme in the metabolic pathway is modified by a reaction product, as is seen in figure 1. The use of regulatory control by Hatzimanikatis et al. to describe metabolic pathways does not distinguish the methodology from the instant application which refers to reversible and irreversible reactions and also applies mixed integer linear programming. Both descriptions result in the identification of enzymatic points in a metabolic pathway the modification of which will alter the performance of the metabolic pathway to realize a maximization of a performance of the metabolic network or pathway. Hatzimanikatis et al. shows that improvements in the product yield, rate of production, and final product concentration are common goals in achieving more efficient and cost-effective bioprocesses (p. 1277, col. 1). Hatzimanikatis et al. shows that recent advances in recombinant DNA technology make targeted modifications in the DNA of an industrial microorganism possible (p. 1277, col. 1-2). Hatzimanikatis et al. explicitly show modification to over-express enzymes of metabolic pathways. With respect to the

argument that Hatzimanikatis et al. teaches away from coupling cellular and bioengineering objectives, the argument is not persuasive. In fact, Hatzimanikatis et al. shows that no improvement in the selectivity for the reference state could be achieved only by enzyme overexpression, without having an effect on the growth rate (p. 1284, col. 2). Thus, Hatzimanikatis et al. suggest growth rate is coupled to amino acid production. Applicant's support that Hatzimanikatis et al. teaches away form coupling cellular objectives, such as growth rate, and bioengineering objective, such as metabolic product production is not persuasive. Hatzimanikatis et al. teaches an interest in studying how modification of expression levels and of the properties of the enzymes that catalyze these reactions affect metabolic functions of the system, such as metabolite concentrations, fluxes, and specific growth rate. Hatzimanikatis et al. shows that in the formulation of the problem the growth rate is maintained at its steady state value. Taken together, Hatzimanikatis et al. does not teach away from coupling bioengineering and cellular objectives.

Applicant argues, based on the argument that Hatzimanikatis et al. teaches away from coupling of bioengineering and cellular objectives, one of ordinary skill would not have been motivated to modify the mixed integer linear programming functions of Hatzimanikatis et al. with the bi-level MILP functions of Bhaskar et al. This is not persuasive because Hatzimanikatis suggests that growth and metabolite production are linked or coupled, especially for amino acid synthesis and shows the formulation of a problem under steady state growth conditions. Even if, for the sake of argument, Hatzimanikatis et al. shows that growth rate and the production of a metabolite are

separate problems, Bhaskar et al. shows that optimal solutions can be found in divergent objective functions.

Claims 1, 2, 4, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hatzimanikatis et al. , in view of Bhaska et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above, and further in view of Yang et al.

The claims are drawn to a method comprising selecting a bioengineering objective function; selecting a cellular objective function forming a linear optimization problem that couples the cellular objective function with the bioengineering objective function; and solving the linear optimization problem to yield a candidate. In an embodiment the bioengineering objective function is lactate overproduction and acetate kinase is targeted for deletion. In an embodiment, a bioengineering objective function is underproduction of a chemical. In an embodiment, the candidate is used to genetically modify the organism.

Hatzimanikatis et al., in view of Bhaska et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above shows a method comprising selecting a bioengineering objective function; selecting a cellular objective function forming a linear optimization problem that couples the cellular objective function with the bioengineering objective function; and solving the linear optimization problem to yield a candidate.

Hatzimanikatis et al., in view of Bhaska et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above does not show an embodiment in which the

bioengineering objective function is lactate overproduction and acetate kinase is targeted for deletion.

Yang et al. shows an embodiment in which the bioengineering objective function is lactate overproduction (p. 32, col. 1) and acetate kinase is targeted for deletion (p. 27, col. 1). In an embodiment, Yang et al. shows a bioengineering objective function that is underproduction of a chemical, specifically acetate (p. 27, col. 1). In an embodiment, Yang et al. shows that the candidate is used to genetically modify the organism (p. 32, col. 1). Yang et al. shows the reduction of acetate production is of primary concern in fermentation and recombinant protein production by *E. coli* (p. 26, col. 2). Yang et al. shows that a reduction in acetate production has been shown to enhance recombinant protein production (p. 27, col. 1).

It would have been obvious to one of skill in the art to modify the method of determining gene candidates for alteration in an organism of Hatzimanikatis et al. , in view of Bhaska et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above to include the bioengineering objectives of Yang et al. because Yang et al. shows that a reduction in acetate production has been shown to enhance recombinant protein production is a primary concern in fermentation and recombinant protein production arts.

Response to Arguments

Applicant's arguments filed 05 August 2008 have been fully considered but they are not persuasive. Applicant argues that Yang et al. does not cure the deficiencies of Hatzimanikatis et al. in view of Bhaskar et al. The argument is not persuasive because

Hatzimanikatis et al. in view of Bhaskar et al. shows a method of identifying modifications to a metabolic pathway by solving a linear optimization problem.

Claims 1, 5, 7-8, 10-14, and 19-20 rejected under 35 U.S.C. 103(a) as being unpatentable over Burgard et al. (Biotechnology and Bioengineering. 2001 74:364-375), in view of Bhaska et al. (Reviews in Chemical Engineering, Volume 16, Issue 1, p. 1-54, 2000).

The claims are drawn to a method comprising selecting a bioengineering objective function; selecting a cellular objective function forming a linear optimization problem that couples the cellular objective function with the bioengineering objective function; and solving the linear optimization problem to yield a candidate. In an embodiment the bioengineering objective function is lactate overproduction and acetate kinase is targeted for deletion. In an embodiment, a bioengineering objective function is underproduction of a chemical. In an embodiment, the candidate is used to genetically modify the organism.

Burgard et al. teach a method of identifying gene candidates for deletion and addition by forming and solving an optimization problem that involves a bioengineering objective and a cellular objective ("Mathematical modeling of gene additions/deletions", p367-369). With respect to the limitation of claim 7, drawn to a candidate deletion and a binary value specifying if a reaction is active or inactive, is also taught by Burgard et al. Burgard et al. teach the use of a binary value to specify if a reaction is active or inactive, "the binary parameter, a_{jk}, is defined to describe which enzymes are coded for by which

genes: a_{jk} = 0 if gene k has no direct effect on reaction j; 1 if gene k codes for an enzyme catalyzing reaction j ("binary parameter", p367-368, Burgard et al.). This reads on the limitation of claim, the assignment of a binary value to a reaction flux. The limitation of deletions is taught in, "In this study we explore what is the smallest gene set capable of maximizing biomass production on glucose substrate (uptake 10mmol) and what is the maximum number of gene deletions from this gene set that still maintains a specified level of biomass production (p.369)". The above statement also teaches the limitations of claim 13 drawn to the evaluation of performance limits ("smallest gene set"), the limitations of claim 20 and 14, drawn to an objective corresponding to maximizing growth rate, and the limitations of claim 5, drawn to growth ("maximizing biomass production"). The title of Burgard et al. also reads on the limitations of claim 13, performance limits. With respect to the limitations of claim 11, drawn to a chemical uptake constraint, is also taught by Burgard et al., "quantifies the network's uptake (if negative) or secretion (if positive) of metabolite i. (p. 366)" and "stoichiometric coefficient of metabolite i (p.366)". With respect to the limitation of claim 12, drawn to quantifying the cellular objective as an aggregate flux, is also taught by Burgard et al. as "maximized the biomass production flux, $v_{max\ biomass}$. The solution yields the maximum theoretical level of biomass production ($v_{max\ biomass}$ = 1.25g biomass/gDW·h) achievable by the metabolic network within the stoichiometric constraints (p. 369)". With respect to the limitation of claim 10, drawn to at least one stoichiometric, is also taught by Burgard et al. in "These upper bounds are set by maximizing the given flux n_j subject to the stoichiometric constraints (p. 369)". With respect to the limitations of claim 19 are

intrinsic to the teaching of Burgard et al., "These problems are solved using CPLEX 6.6 accessed via the commercial software package GAMS. Problems with up to 3700 binary variables were solved on an IBM RS6000-270 workstation (p. 369)".

Burgard et al. do not teach the generation of a bilevel optimization problem or the coupling of cellular and biengineering objective functions.

Bhaskar et al. shows that multiple objective optimization is applied to biochemical engineering problems such as the design of anaerobic digesters (table 1). Bhaskar et al. shows that most real world chemical engineering problems require the simultaneous optimization of several objectives (multiobjective optimization) which cannot be compared easily with each other (are non-commensurate), and so cannot be combined into a single, meaningful scalar objective function (p. 4). Bhaskar et al. shows that objective functions can be coupled through a dual problem such that the dual objective function is always bound to the original objective function called the primal (also known as bi-level) (p. 4-5). Bhaskar et al. shows that if the optimal dual objective function result is identified then the primal objective function result has also been identified (p. 5).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the linear programming and objective functions to predict metabolic pathway alterations of Burgard et al. with the multi-objective optimization and dual/primal optimization problems of Bhaskar et al. because the technique of bi-level optimization and it's ability to couple objective functions was recognized as part of the ordinary capabilities of one killed in the art. One of skill in the art would have been

capable of applying bi-level optimization to an optimization problem and the results would have been predictable to one of skill in the art. This is also supported by applicant's statement, "the referenced duality theory concepts were well known to those skilled in the art" (see remarks p.6, filed 31 October 2007). It would have been further obvious to one of ordinary skill in the art to modify the optimization problems of Burgard et al. to identify gene deletions that couples bioengineering, such as metabolite production, and cellular, such as growth rate, objective functions for an organism because Burgard et al. shows that an optimization problem can be formulated to optimize metabolite production and growth and suggests that the optimization can be used to identify gene deletions as well as gene additions. One of ordinary skill in the art would have been motivated to find genetic modifications, whether gene deletions or additions, that would allow the maximal production of any commercially relevant metabolite product such that growth rate or some other cellular objective is maximized because an organism having such properties would provide the benefit of higher product yields at lower growth costs.

Response to Arguments

Applicant's arguments filed 05 August 2008 have been fully considered but they are not persuasive. Applicant argues that Burgard et al., in view of Bhaska et al. does not teach a method of selecting a bioengineering objective function and a cellular objective function to identify deletions. This is not persuasive because Burgard et al. show the identification of mathematically optimal reaction pathways to recombine into the E. coli metabolic network to optimize amino acid formation for growth on glucose

and acetate (p. 371, col. 1). Burgard et al. shows the proposed optimization framework provides a quantitative means to study metabolic network performance in response to gene deletions (p.373, col. 2). Burgard suggests the framework can be used to suggest promising gene deletion candidates (p. 374, col. 2). With respect to applicants argument that Burgard et al. separately teaches forming an optimization problem to maximize a bioengineering objective and an optimization problem to maximize a cellular objective provides the desirability to form a multi-objective optimization problem of Bhaskar et al., the argument is not persuasive. One of ordinary skill in the art would have been motivated to find genetic modifications, whether gene deletions or additions, that would allow the maximal production of any commercially relevant metabolite product such that growth rate or some other cellular objective is maximized because an organism having such properties would provide the benefit of higher product yields at lower growth costs.

Claims 1-4, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burgard et al. in view of Bhaska et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above, and further in view of Yang et al.

The claims are drawn to a method comprising selecting a bioengineering objective function; selecting a cellular objective function forming a linear optimization problem that couples the cellular objective function with the bioengineering objective function; and solving the linear optimization problem to yield a candidate. In an embodiment the bioengineering objective function is lactate overproduction and acetate kinase is targeted for deletion. In an embodiment, a bioengineering objective function is

underproduction of a chemical. In an embodiment, a bioengineering objective function is over of a chemical. In an embodiment, the candidate is used to genetically modify the organism.

Burgard et al. in view of Bhaska et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above shows a method comprising selecting a bioengineering objective function; selecting a cellular objective function forming a linear optimization problem that couples the cellular objective function with the bioengineering objective function; and solving the linear optimization problem to yield a candidate.

Burgard et al., in view of Bhaska et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above does not show an embodiment in which the bioengineering objective function is lactate overproduction and acetate kinase is targeted for deletion.

Yang et al. shows an embodiment in which the bioengineering objective function is lactate overproduction (p. 32, col. 1) and acetate kinase is targeted for deletion (p. 27, col. 1). In an embodiment, Yang et al. shows a bioengineering objective function that is underproduction of a chemical, specifically acetate (p. 27, col. 1). In an embodiment, Yang et al. shows a bioengineering objective function that is underproduction of a chemical, specifically lactate (p. 32, col. 1). In an embodiment, Yang et al. shows that the candidate is used to genetically modify the organism (p. 32, col. 1). Yang et al. shows the reduction of acetate production is of primary concern in fermentation and recombinant protein production by *E. coli* (p. 26, col. 2). Yang et al. shows that a reduction in acetate production has been shown to enhance recombinant protein production (p. 27, col. 1).

It would have been obvious to one of skill in the art to modify the method of determining gene candidates for alteration in an organism of Burgard et al. in view of Bhaska et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20 above to include the bioengineering objectives of Yang et al. because Yang et al. shows that a reduction in acetate production has been shown to enhance recombinant protein production is a primary concern in fermentation and recombinant protein production arts.

Response to Arguments

Applicant's arguments filed 05 August 2008 have been fully considered but they are not persuasive. Applicants argue Yang et al. does not cure the deficiencies of Burgard et al. in view of Bhaska et al. as applied to claims 1, 5, 7-8, 10-11, 13-14, 19, and 20. The argument is not persuasive because Burgard et al. in view of Bhaskar et al. is not deficient.

Conclusion

None of the claims are currently in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARLHEINZ R. SKOWRONEK whose telephone number is (571) 272-9047. The examiner can normally be reached on 8:00am-5:00pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/KARLHEINZ R SKOWRONEK/
Examiner, Art Unit 1631

25 November 2008